REMARKS

Claims 58-94 were pending. The Examiner rejected claims 58-61, 62-70, 72-79, 81-87, and 90-94; objected to claims 62, 71, and 80; and allowed claims 88 and 89. The Examiner accepted the drawings filed on March 7, 2003, and requested that Applicants re-submit Figure 8. Applicants have herein amended claims 58, 67, 76, 85, 86, 87, 91 and 92; cancelled claims 81 and 90 without prejudice to further prosecution; and added claims 95-132. Support for the amendments and new claims may be found throughout the specification, e.g., at pages 11, 18, 24, 25, 35, 37, 41-45, 52-56, 56-58, and 75-80. Applicants have also included herewith a formal substitute drawing for Figure 8. No new matter has been added. Accordingly, claims 58-80, 82-89, and 91-132 are pending.

In light of the amendments and the remarks herein, Applicants respectfully request reconsideration and allowance of claims 58-80, 82-89, and 91-132.

Drawings

The Examiner accepted the informal, substitute drawings for Figures 1, 3, 9, 10A-10G, and 12 submitted on March 7, 2003. The Examiner requested a re-submission of Figure 8. Applicants have herein provided a formal substitute drawing for Figure 8. No new matter has been added. Accordingly, Applicants respectfully assert that the present drawing complies with the Examiner's request.

Rejection under 35 U.S.C. § 101

The Examiner rejected claim 90 under 35 U.S.C. § 101 as not being supported by either a specific and substantial asserted utility or a well-established utility. Applicants have herein cancelled claim 90 without prejudice to further prosecution, thereby obviating the rejection. Applicants respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 91-94 as being indefinite under 35 U.S.C. § 112, second paragraph, because the recitation "exogenous polynucleotide" had improper antecedent basis. Applicants have herein amended claims 91-92 to delete the term "exogeneous," thereby obviating the rejections. Accordingly, Applicants respectfully request withdrawal of the rejections.

Rejections under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejected claims 58-61, 63-70, 72-79, 81-87, and 90-94 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. In particular, the Examiner stated that the specification:

> does not describe polynucleotides encoding polypeptides that differ from SEQ ID NO: 2 and still retain its functional activity. The specification . . . indicates that SEQ ID NO:2 has four domains that are typical of cytochrome P450s. As these four domains are present in other cytochrome P450s that catalyze different reactions, the presence of these domains in proteins having more than 43% identity . . . to SEQ ID NO:2 is not an indication that it has the same enzymatic activity (emphasis added). The correlation of the other amino acid sequences of SEQ ID NO:2 to its functional enzymatic activity are not described.

Applicants respectfully disagree with the rejection as applied to the pending claims. The standard for application of the written description requirement in the biotechnology context has recently been clarified. See Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002). In Enzo, the court held that:

> [i]t is not correct, however, that all functional descriptions of genetic material fail to meet the description requirement. . . . In its Guidelines, the PTO has determined that the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.' . . . We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement.

Id. at 964.

As presently amended, independent claims 58, 76, and 86 recite polynucleotides, transgenic plants, and methods, respectively, comprising a nucleic acid encoding a polypeptide having greater than 43% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, 60% or greater sequence identity to domain A of SEQ ID NO:2, 60% or greater sequence identity to domain B of SEQ ID NO:2, where the polypeptide is effective for catalyzing the hydroxylation of campestanol. Similarly, independent claims 67, 85, and 87 recite polynucleotides, transgenic plants, and methods, respectively, comprising a nucleic acid encoding a polypeptide having greater than 43% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, 60% or greater sequence identity to domain A of SEQ ID NO:2, 60% or greater sequence identity to domain B of SEQ ID NO:2, where the polypeptide is effective for catalyzing the hydroxylation of 6-oxocampestanol. The present claims therefore expressly recite a particular function: that the encoded polypeptides be effective for catalyzing either the hydroxylation of campestanol (claims 58, 76, and 86) or the hydroxylation of 6-oxo-campestanol (claims 67, 85, and 87). In addition, the claims expressly recite particular structures: that the polypeptides have more than 43% identity to the amino acid sequence set forth in SEQ ID NO:2, 60% or greater sequence identity to domain A of SEQ ID NO:2, and 60% or greater sequence identity to domain B of SEQ ID NO:2. Thus, Applicants have claimed polynucleotides encoding polypeptides having specific functional and structural characteristics.

One having ordinary skill in the art would have recognized that, at the time the application was filed, Applicants had possession of and had invented the full scope of the invention as presently recited, because the specification supports the recited functional and structural characteristics and discloses the relationship between the recited functional and structural characteristics. For example, with respect to the functional (e.g., enzymatic activity) limitations, on page 25 of the specification the term "DWF4 polypeptide" is defined to include a polypeptide that is derived from a 22α-hydroxylase that functions in the brassinolide (BL) biosynthetic pathway. The specification notes that the term encompasses mutants and fragments of the native DWF4 sequence so long as the protein functions for its intended purpose. Pages 40-41 of the specification sets forth physical and biochemical methods to detect enzyme activity

of the polypeptides, including cell elongation measurements and enzymatic assays to measure reaction products and by-products from various substrates in feeding experiments. Pages 41-42 describe a characteristic DWF4 phenotype as including any activity that is exhibited by the native DWF4 polypeptide, including enzymatic and substrate binding activities. The specification goes on to list 11 examples of DWF4 activities on page 42 (activities (a)-(k)). Finally, pages 67-71 set forth growth and feeding experiments to identify enzymatic activities in biosynthetic BR pathways.

The specification also provides adequate written description for the recited structural limitations and provides a correlation of these structural limitations with the previously described functional (enzymatic) limitations. With respect to structure, the specification states on page 18 that polynucleotides or polypeptides of the invention can demonstrate various percentage ranges of sequence identity "over a defined length of the molecules." Page 42 notes that a DWF4 analog can be a derivative, fragment, or fusion of native DWF4 polypeptides and that such analogs preferably exhibit some sequence identity to the native DWF4 polypeptide sequence. Derivatives can include changes within the domains, motifs, or consensus regions of the DWF4 polypeptide. Page 43 notes that another class of analogs includes those that include a DWF4 polypeptide that differs from the native sequence in a domain of interest, such as an analog that exhibits increased sterol binding through optimized sterol binding domain sequences. Page 43 goes on to state that DWF4 polypeptides can include fragments comprising one or more P450 domains or regions.

More particularly, Example 3 describes in detail the four characteristic domains of P450 proteins. Page 53 notes that Domain A binds substrate (e.g., enzymatic substrate) and molecular oxygen, while domain B is known as the steroid binding domain. Figures 2B, 3A, and 3B set forth the relative positions (and sequences) of these domains for the DWF4 polypeptide and other P450 proteins. Importantly, Example 3 also discusses the classification of P450 proteins based on sequence identity, noting that DWF4 and CPD represent different subfamilies of P450 proteins. Such a classification system was well-known to those of ordinary skill in the art at the time of the present application filing; see the IDS filed concurrently herewith for examples of

review articles outlining this classification system. For example, the Nebert *et al.* DNA and Cell Biology Vol. 10 (1) (1991) reference sets forth the accepted delineation of P450 proteins among families, subfamilies, and allelic variants. A P450 protein sequence from one gene family is defined as having $\leq$ 40% identity to that from any other family. Sequences having greater than 40% identity but less than 55% identity are members of different subfamilies (e.g., DWF4 and CPD), while sequences having greater than 55% identity are members of the same subfamily. Sequences having $\geq$ 97% sequence identity are defined as allelic variants.

Given such a well-known classification system, Applicants note that the present claims recite that the claimed polypeptides have greater than 43% sequence identity to SEQ ID NO:2 -- thus reciting members of the DWF4 subfamily as opposed to the CPD subfamily. Furthermore, the present claims recite that the claimed polypeptides have 60% or greater sequence identity to domains A and B of SEQ ID NO:2, thus requiring domains A and B to exhibit a higher than subfamily level of sequence identity to the native DWF4 polypeptide. As noted in the specification, domains A and B perform particular enzymatic functions – domain A is a substrate and molecular oxygen binding domain, while domain B is a steroid binding domain. As there is not an additional classification level between subfamily and allelic variant, and as the present claims require higher than subfamily sequence identity in two domains that are involved in enzymatic function, the present claims both expressly and through the domain A and B sequence limitations indicate that the claimed polypeptides perform DWF4 enzymatic activities. As indicated above, the specification discloses such a correlation between structure (e.g., structure of the overall protein and domains A and B) and enzymatic function. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

The Examiner also rejected claim 90 under 35 U.S.C. § 112, first paragraph as not being adequately described in the specification. Applicants have herein cancelled claim 90 without prejudice to further prosecution, thereby obviating the rejection.

In light of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph (written description).

Rejections under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner rejected claims 58-61, 63-70, 72-79, 81-87, and 90-94 under 35 U.S.C. § 112, first paragraph as being not enabled. In particular, the Examiner stated that:

> "[I]t is highly inaccurate to simply assume that all amino acid sequences that have greater than 43% identity with SEQ ID NO: 2 will also share its functional activity. . . . The specification . . . provide[s] no guidance in how the sequence of SEQ ID NO: 2 may be changed without altering the enzymatic activity of SEQ ID NO: 2 . . .. In the absence of further guidance, it would require undue experimentation for one skilled in the art to determine all of the changes that can be sustained by SEQ ID NO: 2 without altering its ability to catalyze the hydrozylation of campestanol and 6-oxocampestanol.

Applicants respectfully disagree. As noted above, independent claims 58, 76, and 86 recite polynucleotides, transgenic plants, and methods, respectively, comprising a nucleic acid encoding a polypeptide having greater than 43% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, 60% or greater sequence identity to domain A of SEQ ID NO:2, 60% or greater sequence identity to domain B of SEQ ID NO:2, where the polypeptide is effective for catalyzing the hydroxylation of campestanol. Similarly, independent claims 67, 85, and 87 recite polynucleotides, transgenic plants, and methods, respectively, comprising a nucleic acid encoding a polypeptide having greater than 43% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, 60% or greater sequence identity to domain A of SEQ ID NO:2, 60% or greater sequence identity to domain B of SEQ ID NO:2, where the polypeptide is effective for catalyzing the hydroxylation of 6-oxocampestanol.

Contrary to the Examiner's assertions, Applicants have not assumed that all amino acid sequences having greater than 43% amino acid identity with SEQ ID NO: 2 will also share the functional activities of hydroxylating campestanol or 6-oxocampestanol. Instead, Applicants have claimed only those polypeptides having the recited structural limitations that also maintain a particular enzymatic function, e.g., are effective for hydroxylating campestanol or 6-oxocampestanol. For example, the claims require that the recited polypeptides be members of the DWF4 subfamily, which is a different P450 subfamily than CPD. In addition, as noted

above, the claims recite higher than subfamily sequence identity for domains A and B of the polypeptides – domains which are known to have important substrate and steroid binding enzymatic functions.

Pages 40-41 of the specification set forth physical and biochemical methods to detect enzymatic activities of polypeptides, including methods for measuring cell elongation and enzymatic assays to measure reaction products and by-products from various substrates in feeding experiments. Pages 67-71 set forth growth and feeding experiments to identify enzymatic activities and the role of DWF 4 polypeptides in biosynthetic BR pathways. Example 9 at page 67 of the specification describes protocols to determine if a polypeptide performs a similar function in a BR biosynthetic pathway as DWF4. Pages 72-73 set forth a method for spray transformation of host plants, while pages 74-75 describes methods for localizing DWF4 transcription and BR biosynthesis in transformed plants. Methods for histological and/or morphological analysis of transformed plants are also set forth in the Examples and are routinely practiced by those of ordinary skill in the art. Given the guidance provided in the specification, no more than routine experimentation is required for one of skill in the art to identify polypeptides having the requisite activities. Accordingly, Applicants respectfully assert that the pending claims are enabled under 35 U.S.C. § 112, first paragraph.

The Examiner also rejected claim 90 as not being enabled. As Applicants have cancelled claim 90 without prejudice to further prosecution, this rejection is moot. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner also rejected claims 91 and 92 as not being enabled. As suggested by the Examiner, Applicants have herein amended claim 91 and 92 to recite "a plant or bacterial host cell." Accordingly, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

In light of the amendments and the remarks herein, Applicants respectfully request reconsideration and allowance of the pending claims. The Examiner is invited to telephone the under-signed if such would expedite prosecution.

Enclosed is a $534.00 check for the Excess Claims Fee and for the Petition for Extension of Time fee, excess claims fee, and multiple dependent claim fee. Also enclosed is a $180.00 check for the fee for submission of an Information Disclosure Statement filed herewith. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 10/28/2003

Teresa A. Lavoie

Teresa A. Lavoie, Ph.D.
Reg. No. 42,782

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

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